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Prognostic Features and Long-Term Outcome in Patients with Isolated Fetal Ventriculomegaly

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Keywords
Cerebral ventriculomegaly · Prenatal diagnosis · Prenatal counseling · Fetus · Neurosonography · Fetal magnetic resonance imaging · Developmental outcome

Abstract
Objective: In order to provide aid for prenatal counseling in fetal isolated ventriculomegaly (IVM) on ultrasound, we recorded the latest long-term clinical and imaging outcomes of children with a mean age of 7.2 years (range 2.1–14.6). ***Methods:*** In 72 fetuses with IVM, diagnosed between 1999 and 2011, the measurement quality of atrial diameter was reviewed in the axial plane. We assessed the association of characteristics of IVM with outcome parameters in the cohort and in subgroups. Prognostic values of significant associations were reported by receiver operating characteristic curve analysis. ***Results:*** Cerebral anomalies were diagnosed postnatally in 42% and genetic disorders in 12% of 45 live births. Significant associations of outcome parameters were found between the degree of IVM and genetic disorders ($p = 0.017$) with an area under the curve (AUC) of 0.866, and between progression of IVM and motor impairment ($p = 0.024$) with an AUC of 0.789. No significant correlation was found with the other assessed outcome parameters. Furthermore, our subgroup analysis clearly showed that, if cerebral or genetic anomalies are not found postnatally, a favorable outcome may be expected. ***Discussion:*** Diameter and progression in IVM are not significantly associated with most outcome parameters. Cerebral anomalies and genetic disorders may contribute to an unfavorable outcome.

Introduction

Counseling parents after the diagnosis of fetal ventriculomegaly (VM) is a challenge because of the uncertainty of neurodevelopmental outcome, and this may lead to discussion about termination of pregnancy (TOP). Studies reported TOP rates of 3.6% for mild isolated VM up to 52% for severe isolated VM [1–5]. We attempted to provide further evidence to counsel parents with fetuses with isolated VM (IVM) detected at ultrasound.

The primary aim of our study was to identify characteristics of prenatal IVM as predictive factors for adverse postnatal outcome, to determine their predictive value, and to evaluate the accuracy of prenatal sonography by postnatal confirmation and postnatal diagnosis of additional brain anomalies. The secondary aim was the study of subgroups with unfavorable neurodevelopmental outcome due to postnatal detection of additional anomalies.

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Patients and Methods

This was a retrospective cohort analysis. The study was approved by the Swiss Federal Board of Health (protocol No. 035.001-98/172). Signed informed consent was obtained from parents to retrieve children's outcome data.

Identification of Cases

Fetuses with cerebral VM were identified within a 13-year period from January 1999 until December 2011 in a tertiary perinatal care center at University Hospital Zürich. Inclusion criteria were (1) VM of 10 mm or more [6]; (2) gestational age beyond 18th week of pregnancy; (3) postnatal age above 2 years; and (4) parental consent for data collection and completion of our questionnaire. Exclusion criteria were (1) prenatal findings of associated anomaly; (2) technically incorrect measurements; (3) twin pregnancies, complicated by pathology due to monochorionicity with twin-to-twin-transfusion syndrome or selective intrauterine growth retardation with pathological flow interrogation; and (4) premature deliveries with signs of chorioamnionitis. The study population consisted of prenatal IVM.

Antenatal and Obstetric Data Sources and Data Captured

Antenatal and obstetric data were collected from scan reports and clinic charts of the pregnant women. Data captured were gestational age at diagnosis, serial sonograms, prenatally detected associated anomalies, fetal karyotype, maternal infection serologies, maternal platelet antibodies, and characteristics of VM (atrial width in millimeters, intrauterine evolution, symmetry, and laterality). All sonographic still frames were then reviewed by 2 specialized obstetric sonographers (A.W. and J.W.) according to the following protocol: measurements in a transventricular plane at the glomus of the choroid plexus with the calipers inside the ventricular walls [7, 8]. If measurements were performed in an oblique manner, calipers were replaced perpendicular to the ventricular wall and opposite the internal parieto-occipital sulcus. Cerebral lateral ventricles were assessed for laterality, symmetry, progression, and regression. Regression or progression of VM was defined as at least 2 mm difference between serial scans. Asymmetry was defined as at least 2 mm difference between the 2 lateral ventricles. VM was categorized as mild (10–11.9 mm), moderate (12–14.9 mm), and severe (≥15 mm). The category was based on the largest measurement in asymmetry, unilaterality, or at serial scans. All preterm births were searched for chorioamnionitis as a confounder for adverse postnatal outcome.

Postnatal Data Source and Data Captured

Postnatal data were collected from August to December 2013. A detailed follow-up was made in each case by consultation of medical records, cranial ultrasound scans, magnetic resonance imaging (MRI), and developmental and neurological assessments. A Strengths and Difficulties Questionnaire (SDQ) was completed by parents [9], and they were asked about early intervention, occupational therapy, or attendance of a special needs school. Confounding factors (severe disease and accidents) and parental socioeconomic status were also recorded. Prenatal diagnosis was compared with autopsy ($n = 4$) and postnatal imaging ($n = 34$). Cranial ultrasound, brain MRI, and developmental or neurological assessments were performed at the discretion of the pediatrician.

Definition of Outcome

Severe motor impairment was defined as cerebral palsy or progressive myopathy and mild motor impairment as delay in motor skills, balance problems, coordination deficits, and hypotonia. Severe visual impairment was defined as uni- or bilateral blindness and mild visual impairment as squint, myopia, or the necessity to wear glasses. Severe hearing impairment was defined by the need for hearing aids. Learning problems were defined as receipt of early intervention or attendance of a special needs school. Emotional-behavioral outcome was assessed with the SDQ score (normal 0–13, borderline 14–16, and suspicious 17–40), obtaining standardized information about behavior, social skills and integration, hyperactivity, and emotional problems from the age of 3 years onwards. Occupational therapy was used as a surrogate for developmental outcome. Children under 3 years and with severe psychomotor handicap were excluded from behavioral data collection. The instrument is applicable to infants with some degree of developmental delay or handicap. The score was age adjusted. For neonatal cerebral ultrasound, reference values of sonographic ventricular index were used [10]. Socioeconomic status (range 2–11) was calculated according to Largo et al. [11] with a 6-point scale according to paternal occupation and maternal education.

Statistical Analyses

Properties of VM (ventricular diameter, intrauterine evolution, symmetry, and laterality) were modeled on dichotomized or trichotomized scores of outcome parameter categories. Associations between fetal VM and outcome parameters were calculated with Kendall's tau-β exact p values, and values <0.05 were considered as statistically significant. The following outcome parameters were analyzed with trichotomized scores: motor, vision and hearing impairment, and emotional-behavioral problems. The following outcome parameters were analyzed with dichotomized scores: epilepsy, learning problems, need for surgery, occupational therapy, postnatal persistence of VM, postnatal diagnosis of a central nervous system (CNS) malformation, any other congenital malformation, genetic abnormality, and mortality. The prognostic value of fetal ventricular diameter and intrauterine evolution on binary outcomes was assessed using receiver operating characteristic curve analysis. Areas under the curve are reported with 95% confidence interval. Statistical analysis was performed using SPSS Statistics for Mac, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Identification of Cases

Among 50,543 pregnancies, 165 fetuses were referred to the University Hospital Zürich during the study period for detection of VM on ultrasound. Ninety-three fetuses were excluded because of (1) prenatal diagnosis of aneuploidy ($n = 8$); (2) intrauterine infection ($n = 3$); (3) myelomeningocele ($n = 42$); (4) structural cerebral anomaly ($n = 17$), or (5) structural extracerebral malformation ($n = 18$) detected prenatally. In our study population, screening for platelet antibodies was not done consistently ($n = 12/55$), and no case of fetal alloimmune thrombopenia was detected.

The prevalence of twin pregnancies with 1 fetus with VM was 6% (n = 10/165). Three cases of IVM occurred in dichorionic twins. Seven cases of IVM occurred in monochorionic twins; 5 of them were excluded due to feto-fetal transfusion syndrome or growth retardation with pathological flow exams. Finally, 2 monochorionic and 3 dichorionic twin pregnancies remained in the study group, accounting for 9% of confirmed IVM (n = 5/55).

Seventeen (24%) of the remaining 72 cases were excluded because measurement or imaging plane did not correspond with the imaging protocol (Fig. 1). Fifty-five fetuses with confirmed IVM remained in the prenatal follow-up group.

Antenatal and Obstetric Evaluation

There were 20 cases with mild VM, 14 cases with moderate VM, and 21 cases with severe VM (Fig. 2). 78% of the fetuses had bilateral VM (n = 43) and 22% had unilateral VM (n = 12). 65% showed symmetrical VM (n = 36) and 35% asymmetrical VM (n = 19). Serial prenatal ultrasound scans were available in 78% (n = 42/55). 37% presented regression of VM (n = 16), in 33% atrial width remained unchanged (n = 14), and 28% showed progression (n = 12) (Table 1). Forty-five live births (82%, n = 45/55) remained evaluable for follow-up. Among the preterm births, there was no case with evidence of chorioamnionitis (n = 0/5). Parents opted for TOP in 14.6%, all in the moderate or severe VM group. There was no TOP due to mild VM in our study.

Postnatal Evaluation

The median duration of postnatal follow-up was 7.2 years (range 2.1–14.6). The follow-up rate was 93% (n = 43/45) for neurodevelopment and 76% (n = 34/45) for postnatal imaging. Severe motor impairment occurred in 12% of the children (n = 5/42), 4 of them with cerebral palsy. Severe vision impairment occurred in 7% (n = 3/42). Severe hearing impairment occurred in 2% (n = 1/42). Seizures occurred in 17% (n = 7/42). Ventriculoperitoneal shunt implantation or ventriculostomy was performed in 21% (n = 9/42). One quarter of the children had learning problems (n = 10/42), and one quarter received occupational therapy (n = 11/42). Behavior was assessed as abnormal in 7% (n = 2/29). Mild or no motor problems occurred in 14% (n = 6/42) and 74% (n = 31/42), respectively. Mild or no vision impairment occurred in 17% (n = 7/42) and 76% (n = 32/42), respectively. Mild or no hearing impairment occurred in 2% (n = 1/42) and 95% (n = 40/42), respectively. Borderline behavioral problems were found in 10% (n = 3/29) and normal behavior in 86% (n = 25/29).

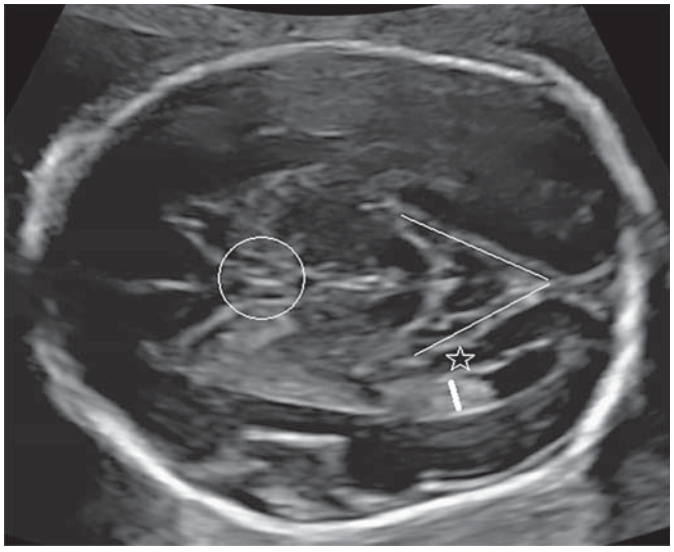

Fig. 1. Standardized measurement according to the study protocol in the transventricular plane with the ambient cistern (convergent lines) and the fornix columns (circle) as landmarks. The calipers are placed at the inner edge of the atrium (fat line), opposite the deepest part of the internal parieto-occipital sulcus (star).

Table 1. Patient characteristics

Maternal age at delivery, years	33.4 (22–45)
Parental socioeconomic status	4.85 (2–11)
Gestational age at diagnosis of VM, weeks	24 (18–35)
Ventricular diameter, mm	17 (10–24)
Intrauterine evolution of VM, mm	+2 (–6 to +20)
Gestational age at birth, weeks	38 (29–41)
Preterm birth[a], n/N (%)	5/45 (11)
Birth weight, g	3,010 (1,025–4,050)
Apgar 5 min	8 (3–10)
Apgar 10 min	9 (7–10)
pH umbilical cord artery	7.26 (7.10–7.38)

Values are means (ranges) unless otherwise specified. VM, ventriculomegaly. [a] Range 29–36 weeks.

Postnatal resolution of VM occurred in 18% (n = 7/38), especially in mild and moderate VM cases. In 1 case with confirmed severe dilatation of 17 mm, VM was resolved at neonatal ultrasound. VM was always confirmed when autopsies in cases of TOP or intrauterine fetal death were done.

Postnatal detection of additional cerebral anomaly occurred in 42% (n = 16/38) whenever postnatal imaging

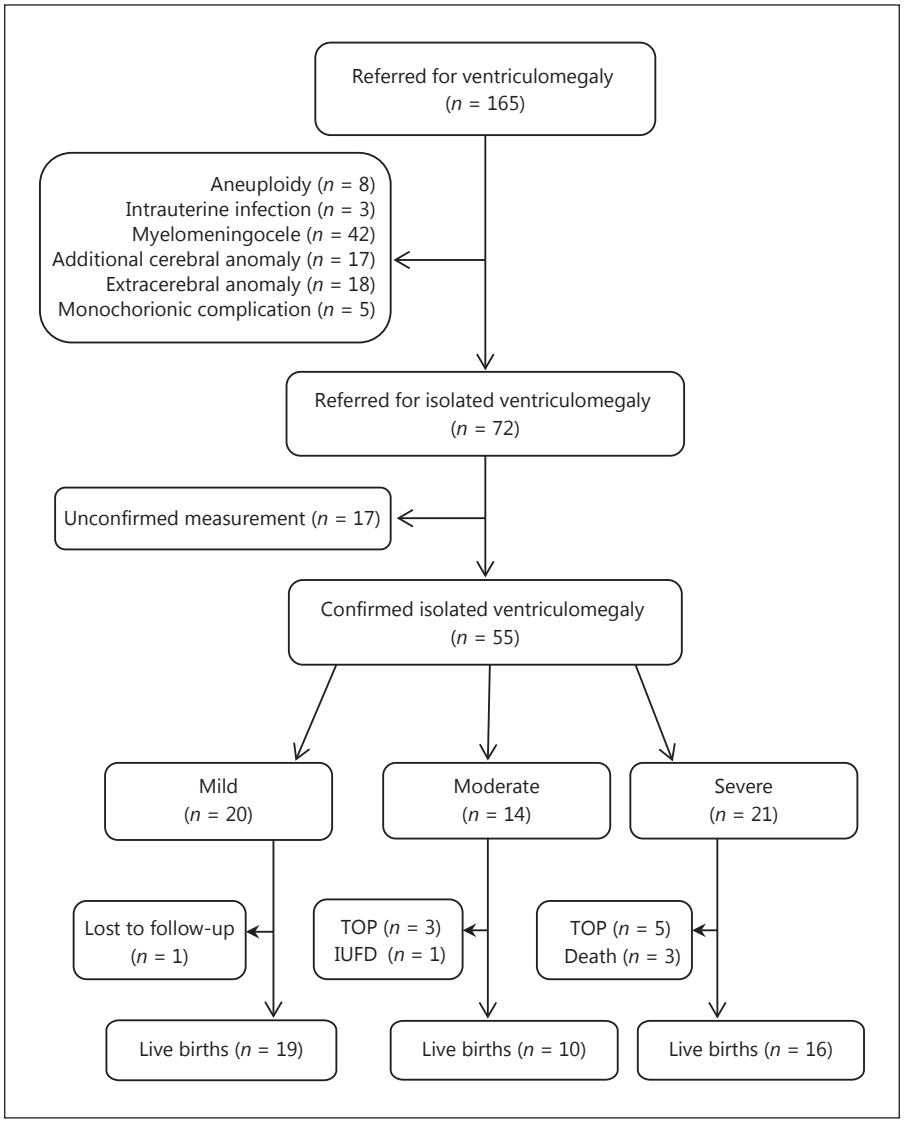

Fig. 2. Inclusion into analysis and follow-up. TOP, termination of pregnancy; IUFD, intrauterine fetal death.

was performed (Table 2). In 10 of 16 cases, the final diagnosis of the cerebral abnormality was only made by brain MRI and not by cranial ultrasound. In 2 cases, the final diagnosis of cerebral anomaly was only made by a repetitive brain MRI at 3 and 8 years, and not by the first MRI at the age of 1 and 10 months, respectively. A quarter of these cases had a genetic syndromic condition ($n = 4/16$).

Postnatal diagnosis of a genetic anomaly was found in 12% ($n = 5/43$). All genetic syndromes (nonnumeric chromosomal anomalies) were in the severe VM subgroup with an atrial width of 24–32 mm (Table 3). There was only 1 case of aneuploidy (trisomy 21 with VM 13 mm), in which prenatal karyotyping was proposed but denied. Noncerebral anomalies were found in 7% ($n = 3/43$): 1 infant with craniosynostosis, 1 with club feet, and 1 with Coats' disease.

One baby died on the first day of life, 1 at 5 months, and 1 at 2 years. Neonatal or infant mortality occurred in 7% ($n = 3/43$) and was found exclusively in the severe fetal VM subgroup with an atrial width of 24–32 mm.

Identification of Prognostic Factors

There was no association between the degree of VM and neurologic outcome variables (motor, vision, and hearing impairment and epilepsy), developmental outcome variables (occupational therapy and learning problems), or emotional-behavioral problems (Table 4). In terms of learning problems, neither a significant associa-

Table 2. Additional brain anomalies diagnosed after birth

Corpus callosum abnormalities	9
Defect of septum pellucidum	6
Migration abnormalities[a]	6
Aqueductal stenosis	6
Cerebellar malformation	7
Hippocampal malformation	3
Tectal malformation	2
Optic nerve hypoplasia	2
Cysts[b]	3
Pontocerebellar hypoplasia	1
Intracranial bleeding	2

Values are *n*. One child may have 1 or more findings. [a] There were 3 heterotopias and 3 polymicrogyrias. [b] There were interhemispheric and arachnoid cysts, and 1 child had multiple cerebellar cysts.

Table 3. Additional genetic anomalies diagnosed after birth

Genetic anomaly	Ventriculomegaly, mm
Muscle eye brain disease	32
Aicardi syndrome	31
Gomez-Lopez-Hernandez syndrome	28
Complex unidentified syndrome	24
Trisomy 21	13

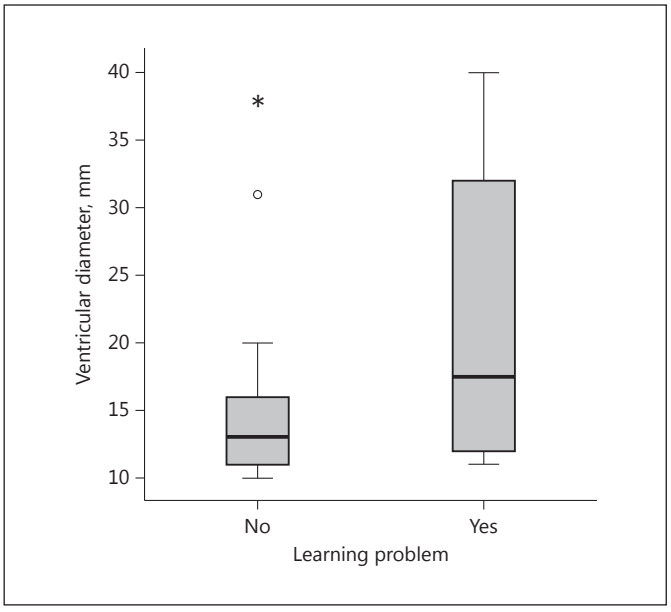

Fig. 3. Box plot for ventricular diameter and learning problems with 2 outliers.

tion nor a cutoff value of ventricular dilatation was identified, and even cases with very severe fetal VM (outliers with VM of 31 and 38 mm) had a good outcome for learning abilities (Fig. 3).

The degree of atrial width was predictive of intrauterine progression ($p = 0.000$), postnatal confirmation by ultrasound or autopsy ($p = 0.029$), need for surgery ($p = 0.003$), and postnatal detection of a genetic anomaly with a significant association ($p = 0.017$). Intrauterine progression was predictive of motor impairment ($p = 0.024$) and need for surgery ($p = 0.005$). Neither ventricular diameter nor intrauterine evolution of VM was associated with symmetry or laterality. Neither symmetry nor laterality was predictive of the assessed outcome parameters.

Presented by receiver operating characteristic curves, the prognostic value of atrial diameter for genetic anomalies had an area under the curve (AUC) of 0.866 (Fig. 4). Atrial diameter of >20 mm during intrauterine follow-up was the best predictor (furthest point from the diagonal line) with a sensitivity of 80% and a specificity of 92%. The prognostic value of intrauterine progression for motor impairment had an AUC of 0.789 (Fig. 5). Any intrauterine progression >0.5 mm was the best predictor with 70% sensitivity and 85% specificity for later mild or severe motor impairment.

Subgroup Analysis

Postnatal detection of an additional cerebral anomaly was significantly associated with motor and vision impairment, seizures, surgery, learning problems, and occupational therapy. Postnatal diagnosis of a genetic abnormality had a significant association with motor impairment and need for occupational therapy, even though in a lower degree than in children with postnatal detection of additional cerebral anomalies (Table 5). Accordingly, the overall group emotional-behavioral problems were neither associated with cerebral nor with genetic anomalies. The absence of a postnatal additional CNS or genetic finding in children with unselected prenatal VM was associated with good outcomes, except for hearing impairment and behavioral outcome and irrespective of severity or progression of VM. Even though the postnatal finding of a genetic or cerebral anomaly is a predictor of outcome, these postnatal diagnoses were not significantly associated with prenatal degree of VM nor with prenatal progression of VM.

Table 4. Association of degree and evolution of fetal VM with outcome variables

	Intrauterine degree of VM				Intrauterine evolution of VM			
	mild	moderate	severe	association	regression	stability	progression	association
Motor impairment								
No	15 (83)	8 (80)	8 (57)	0.22 (ns)	13 (87)	10 (83)	4 (40)	0.34* (p = 0.024)
Mild	1 (6)	2 (20)	3 (21)		1 (7)	1 (8)	4 (40)	
Severe	2 (11)	0 (0)	3 (21)		1 (7)	1 (8)	2 (20)	
Vision impairment								
No	15 (83)	8 (80)	9 (64)	0.16 (ns)	12 (80)	10 (83)	6 (60)	0.13 (ns)
Mild	2 (11)	1 (10)	4 (29)		1 (7)	2 (17)	3 (30)	
Severe	1 (6)	1 (10)	1 (7)		2 (13)	0 (0)	1 (10)	
Hearing impairment								
No	16 (89)	10 (100)	14 (100)	0.22 (ns)	15 (100)	10 (83)	10 (100)	0.06 (ns)
Mild	1 (6)	0 (0)	0 (0)		0 (0)	1 (8)	0 (0)	
Severe	1 (6)	0 (0)	0 (0)		0 (0)	1 (8)	0 (0)	
Seizures								
No	15 (83)	10 (100)	10 (71)	0.11 (ns)	14 (93)	10 (83)	7 (70)	0.24 (ns)
Yes	3 (17)	0 (0)	4 (29)		1 (7)	2 (17)	3 (30)	
Surgery								
No	17 (94)	9 (90)	7 (50)	0.43* (p = 0.003)	14 (93)	11 (92)	4 (40)	0.45* (p = 0.006)
Yes	1 (6)	1 (10)	7 (50)		1 (7)	1 (8)	6 (60)	
Learning problems								
No	15 (83)	8 (80)	9 (64)	0.18 (ns)	13 (87)	10 (83)	5 (50)	0.30 (ns)
Yes	3 (17)	2 (20)	5 (36)		2 (13)	2 (17)	5 (50)	
Occupational therapy								
No	15 (83)	8 (80)	8 (57)	0.23 (ns)	12 (80)	10 (83)	5 (50)	0.23 (ns)
Yes	3 (17)	2 (20)	6 (43)		3 (20)	2 (17)	5 (50)	
Emotional-behavioral problems								
No	11 (92)	5 (83)	9 (82)	0.09 (ns)	7 (78)	9 (90)	6 (100)	0.24 (ns)
Borderline	0 (0)	0 (0)	2 (18)		1 (11)	0 (0)	0 (0)	
Severe	1 (8)	1 (17)	0 (0)		1 (11)	1 (10)	0 (0)	
Persistence of VM after birth								
No	4 (36)	2 (25)	1 (5)	0.34* (p = 0.029)	3 (27)	2 (22)	1 (8)	0.20 (ns)
Yes	7 (64)	6 (75)	18 (95)		8 (73)	7 (78)	11 (92)	
Additional brain anomaly diagnosed after birth								
No	6 (55)	6 (75)	10 (53)	0.05 (ns)	7 (64)	6 (67)	5 (42)	0.20 (ns)
Yes	5 (46)	2 (25)	9 (47)		4 (36)	3 (33)	7 (58)	
Genetic anomaly diagnosed after birth								
No	18 (100)	9 (90)	11 (73)	0.34* (p = 0.017)	12 (75)	10 (77)	5 (42)	0.25 (ns)
Yes	0 (0)	1 (10)	4 (27)		4 (25)	3 (23)	7 (58)	
Mortality								
No	18 (100)	10 (100)	13 (81)	0.30 (p = 0.058)	15 (100)	12 (92)	9 (82)	0.26 (ns)
Yes	0 (0)	0 (0)	3 (19)		0 (0)	1 (8)	2 (18)	
Intrauterine evolution of atrial width								
Regressive	10 (50)	4 (50)	2 (14)	0.49* (p = 0.000)				
Stable	10 (50)	2 (25)	2 (14)					
Progressive	0 (0)	2 (25)	10 (71)					

Values are n (%). VM, ventriculomegaly; ns, not significant. * Significance with Kendall's tau-β exact p values <0.05.

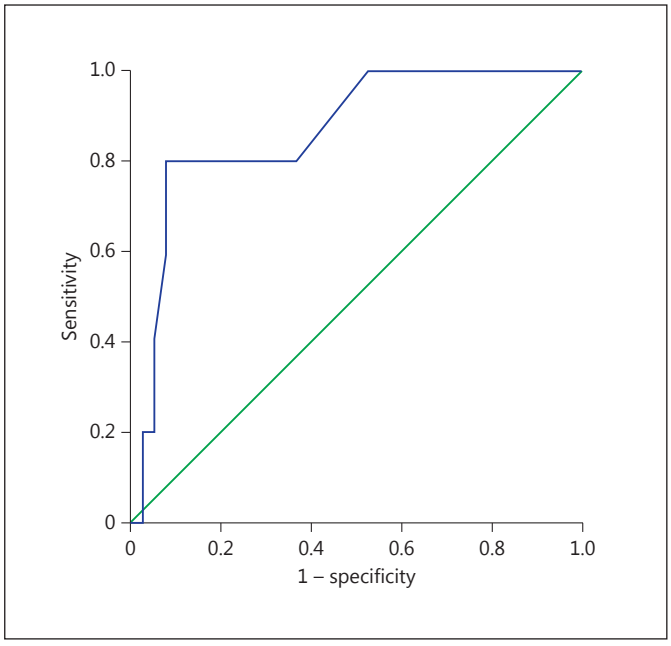

Fig. 4. Receiver operating characteristic curve of prognostic value of ventricular diameter (mm) for the diagnosis of a genetic anomaly after birth. Area under the curve 0.866 (95% CI 0.708–1.000).

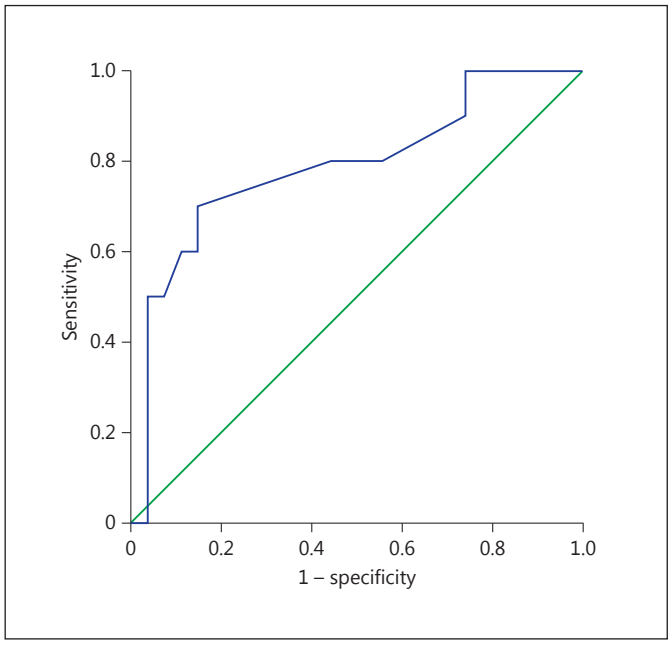

Fig. 5. Receiver operating characteristic curve of prognostic value of intrauterine increase or decrease (mm) of isolated ventriculomegaly for motor impairment. Area under the curve 0.789 (95% CI 0.609–0.968).

Discussion

Our data, in accordance with most of the literature, show that the degree of fetal IVM per se was not correlated with neurodevelopmental outcome, behavioral problems, or postnatal detection of brain anomalies (Table 4) [1–3, 12–18]. Fetal atrial diameter could not predict learning problems (Fig. 3). Some studies described higher incidences of neurodevelopmental delay in severe IVM by calculating prevalence differences in percentages without data about statistical significance [4, 19–23].

In this study, atrial diameter, however, was significantly associated with postnatal detection of genetic abnormalities (Table 4). We show, for the first time, its predictive value for the likelihood of an underlying genetic defect (Fig. 4). This corroborates published registry data, population-based data, and a prospective study [1–3, 22] where genetic syndromes accounted for most of the genetic anomalies in live born infants with severe VM >15 mm.

The positive association of intrauterine progression of VM with motor impairment (Table 4) is in line with earlier reviews and studies [12, 15, 24]. Only in 1 study, the course of mild to moderate VM did not influence neurological outcome [13]. To our knowledge, we present, for the first time, the prognostic value of any intrauterine progression for motor impairment (Fig. 5).

The spectrum of postnatally diagnosed additional brain anomalies was different from that of a meta-analysis, where corpus callosal abnormalities and defects of the septum pellucidum were not reported [25] (n = 34), but similar to population-based data [2] and studies that incorporated fetal MRI [3, 13, 26] (Table 2).

Our high rate of postnatally diagnosed additional brain anomalies differed from other data with a range of 7–17% [1, 2, 26]. In our study, most of the postnatally diagnosed brain anomalies were detected on postnatal MRI, which is in line with higher detection rates in postnatal MRI compared to postnatal ultrasound in other articles [21, 25]. Some brain anomalies in our cohort were only found on MRI after 1 year, which corresponds with the observation of Falip et al. [13]. The high proportion of postnatally diagnosed brain anomalies may be explained firstly by our long-term follow-up of brain imaging and the continuing pre- and postnatal development of the brain. Some lesions may only be detectable after the neonatal period. Secondly, we could not include extended fetal neurosonography nor fetal MRI in our study, as imple-

Table 5. Association of outcome variables with postnatal additional cerebral findings and postnatal diagnosis of a genetic anomaly

	Postnatal finding of CNS abnormality			Postnatal finding of genetic abnormality			Neither postnatal CNS nor postnatal genetic finding		
	no	yes	association	no	yes	association	no	yes	association
Motor impairment									
No	26 (96)	5 (33)	0.67* ($p = 0.000$)	31 (82)	0 (0)	0.53* ($p = 0.022$)	5 (31)	26 (100)	0.73* ($p = 0.000$)
Mild	1 (4)	5 (33)		4 (11)	2 (50)		6 (38)	0 (0)	
Severe	0 (0)	5 (33)		3 (8)	2 (50)		5 (31)	0 (0)	
Vision impairment									
No	24 (89)	8 (53)	0.39* ($p = 0.016$)	31 (82)	1 (25)	0.38 (ns)	8 (50)	24 (92)	0.46* ($p = 0.003$)
Mild	2 (7)	5 (33)		5 (13)	2 (50)		6 (38)	1 (4)	
Severe	1 (4)	2 (13)		2 (5)	1 (25)		2 (13)	1 (4)	
Hearing impairment									
No	26 (96)	14 (93)	0.07 (ns)	36 (95)	4 (100)	0.07 (ns)	15 (94)	25 (96)	0.06 (ns)
Mild	1 (4)	0 (0)		1 (3)	0 (0)		0 (0)	1 (4)	
Severe	0 (0)	1 (7)		1 (3)	0 (0)		1 (6)	0 (0)	
Seizures									
No	27 (100)	8 (53)	0.60* ($p = 0.001$)	33 (87)	2 (50)	0.29 (ns)	9 (56)	26 (100)	0.57* ($p = 0.001$)
Yes	0 (0)	7 (47)		5 (13)	2 (50)		7 (44)	0 (0)	
Surgery									
No	25 (93)	8 (53)	0.46* ($p = 0.006$)	32 (84)	1 (25)	0.42 (ns)	9 (56)	24 (92)	0.43* ($p = 0.009$)
Yes	2 (7)	7 (47)		6 (16)	3 (75)		7 (44)	2 (8)	
Learning problems									
No	26 (96)	6 (40)	0.63* ($p = 0.000$)	31 (82)	1 (25)	0.39 (ns)	6 (38)	26 (100)	0.71* ($p = 0.000$)
Yes	1 (4)	9 (60)		7 (18)	3 (75)		10 (63)	0 (0)	
Emotional-behavioral problems									
No	18 (86)	7 (88)	0.04 (ns)	23 (85)	2 (100)	0.11 (ns)	8 (89)	17 (85)	0.07 (ns)
Borderline	1 (5)	1 (13)		2 (7)	0 (0)		1 (11)	1 (5)	
Severe	2 (10)	0 (0)		2 (7)	0 (0)		0 (0)	2 (10)	
Occupational therapy									
No	25 (93)	6 (40)	0.57* ($p = 0.000$)	31 (82)	0 (0)	0.55* ($p = 0.021$)	6 (38)	25 (96)	0.65* ($p = 0.000$)
Yes	2 (7)	9 (60)		7 (18)	4 (100)		10 (63)	1 (4)	
Additional brain anomaly diagnosed after birth									
No				15 (56)	1 (20)	0.26 (ns)			
Yes				12 (44)	4 (80)				
Genetic anomaly diagnosed after birth									
No	26 (96)	12 (75)	0.32 (ns)						
Yes	1 (4)	4 (25)							
Mortality									
No	27 (96)	14 (88)	0.17 (ns)	38 (100)	3 (60)	0.61 (ns)	15 (88)	26 (100)	0.27 (ns)
Yes	1 (4)	2 (13)		0 (0)	2 (40)		2 (12)	0 (0)	

Values are *n* (%). CNS, central nervous system; ns, not significant. * Significance with Kendall's tau-β exact *p* values <0.05.

mentation of MRI had only started in 2005 and was not performed systematically. Neurosonography and standardization of necessity and reporting of MRI have made major advances during the study period [27, 28].

Our subgroup analysis determined that postnatally detected brain and genetic anomalies were positively associated with unfavorable outcomes and were important prognostic factors, confirming previous findings [13, 15,

17]. Contrary to other articles, in utero progression was not a significant predictor of cerebral abnormalities diagnosed on postnatal imaging [26, 29].

Conversely, we show, for the first time, a positive association with favorable outcome if IVM remained postnatally truly isolated, in the absence of postnatal findings of additional cerebral or genetic anomalies (Table 5).

Prevalences of fetal IVM, twin pregnancies, and preterm birth in our cohort and distributions of prenatally detected aneuploidies, infections, CNS anomalies, and other anomalies reflect previous study cohorts. A positive association of atrial diameter with postnatal confirmation and intrauterine progression, and a lack of association of symmetry and laterality with later outcome were similar to reported data [1–4, 12, 13, 15, 16, 18, 21–24, 30–32]. Unlike other studies, we deliberately did not exclude twins, unless complications due to placental anastomosis were present, because of a higher incidence of IVM in twins [1, 2, 4, 22, 32]. We confirmed also a 2% rate of regression to normal in severe IVM [2]. A higher neonatal and infant mortality has been described in severe IVM elsewhere [1, 2, 12], but did not reach significance in our cohort ($p = 0.058$), which might be explained by the sample size of life births. Moreover, we were not able to analyze the association of fetal alloimmune thrombocytopenia with VM, as the investigation for platelet antibodies was not performed systematically. However, 11% screen-positive cases for platelet antibodies in a cohort of fetal VM have been reported recently, and no association with prenatal ultrasound findings, such as laterality, symmetry, or progression, was found [33].

Our data emphasize that prenatal counseling should not be based on severity of IVM alone. Categorization into mild, moderate, and severe fetal IVM is also not accurate for prognosis. Apparently, IVM has been discussed as a nonspecific diagnosis, accompanying symptom, or provisional diagnosis of exclusion [15, 28]. After karyotyping and exclusion of an infectious etiology and antibodies against fetal platelets, IVM calls for advanced ultrasound imaging and fetal MRI to detect additional cerebral and extracerebral anomalies. This implies extended neurosonography [7, 32] and targeted search for syndromic disease [34]. Transvaginal scan and 3-dimensional reconstruction further help in the visualization of midline structures, vermis, and brain stem [35]. The cause of VM, whether developmental, disruptive, or obstructive, has an impact on outcome and counseling. Associated brain anomalies, whether secondary to VM or of primary origin, also have an impact on counseling. VM calls for prenatal follow-up, as progression of IVM seems to have a prognostic value for motor impairment, and associated anomalies are not always found in the first examination, as reported by others [12, 15, 18].

Importantly, measurement can be subject to error due to an off-axis plane or improper caliper placement. By application of an image score [8], we excluded these measurements (Fig. 1). Frequent false-positive results have been previously described in mild IVM [1, 2, 36, 37] and may be a bias for outcome analysis.

Variable additional detection rates of 5–66% by intrauterine MRI are reported in the literature [18, 26, 32, 38–40]. The level of experience of the ultrasound examiner was considered as a possible bias. After expert sonography, the additional detection rate of MRI is low [41–43]. MRI may give more information on cortex, optic nerve, brainstem, and acquired parenchymal lesions, such as bleeding, ischemia, or inflammation [32, 37]. At an early gestational age, cortical malformations are not detected due to immaturity of cortical development.

In line with previous reports, our data support that IVM remains a diagnosis of exclusion until the first years of life. Therefore, it is important to perform systematic pre- and postnatal brain MRI, the latter with an adequate interval from birth, to identify additional cerebral anomalies that may impact developmental outcome [13, 15]. Neurodevelopmental follow-up is recommendable, at least until postnatal MRI after a given interval has been performed.

The strengths of our study are the selective inclusion after prenatal image review, the duration of clinical and imaging follow-up, ranging from 2.1 to 14.6 years, and a high follow-up rate of 76 and 93% for neurodevelopment and postnatal imaging, respectively, compared to 60–80% in other publications [1, 3, 18]. Its main limitation is the retrospective design, no inclusion of multiplanar neurosonography or fetal MRI, and no formal neurological or developmental assessment. Few studies were designed prospectively [3, 13] or compared findings with control groups [3, 14, 44] but had a short follow-up. One study reported behavioral problems in asymmetric IVM and lower neuropsychological scores in unilateral IVM at a mean age of 2.7 years. A follow-up of the same cohort 6 years later showed no difference from the general population [44, 45]. In another study, abnormal neurological findings in IVM with and without associated CNS anomalies at 6 months and 1 year had resolved at 2 years [3]. Duration of follow-up may have an impact on results.

We used the need for early intervention and attendance of a special needs school as a surrogate marker for

learning problems and occupational therapy as a surrogate marker for development. This may be a bias, as the awareness about prenatal findings may favor recommendations for rehabilitation therapies [3, 44].

There is a need for further prospective studies on this topic, based on defined neurosonography protocols with fetal follow-up, fetal and postnatal MRI with an adequate interval from birth, application of formal neurological and developmental tests with control groups until school age, and application of uniform definitions of neurodevelopmental delay.

In conclusion, the prognosis in a fetus with stable IVM remains difficult, as outcome may be favorable irrespective of its degree. Nevertheless, fetuses with severe VM are more likely to have underlying genetic syndromes with a higher risk of adverse outcomes.

Disclosure Statement

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